

Remarks

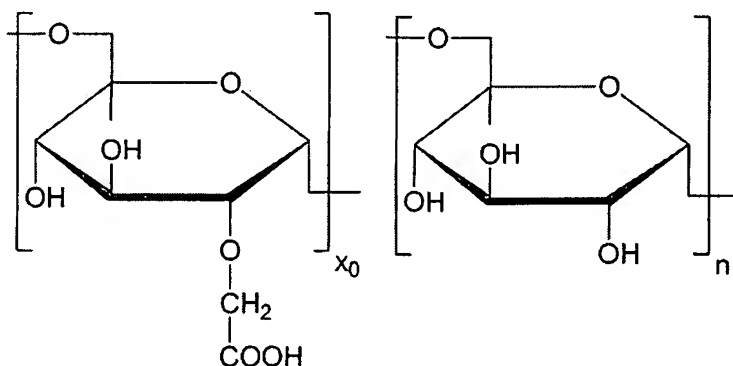
Claim 65 is pending. Claim 65 is currently amended. Claim 69 is new. Support for the amendments and new claim can be found at, for example, the last paragraph on page 5 through the top of page 10 and Example 2 spanning pages 28-41, as well as Figs. 5 and 9 of the originally filed application. Claim 65 is rejected.

At the outset, the Applicants wish to thank the Examiner for the helpful interview of February 17, 2009 in which the rejections under 35 USC §112 and related issues were discussed. This Response is consistent with the helpful guidance provided by the Examiner during the interview.

Claim 65 is rejected under 35 USC §112, second paragraph, as indefinite.

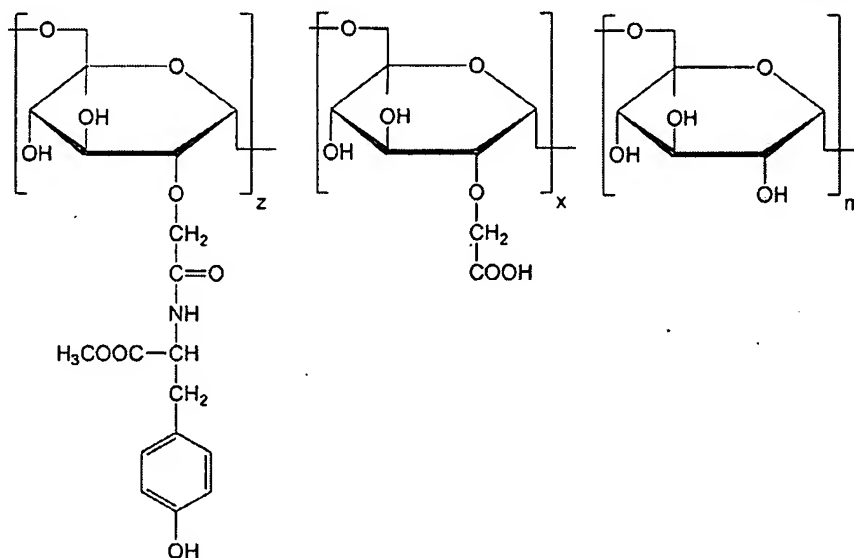
Amended Claim 65 is definite under 35 USC §112, second paragraph, and supported by the originally filed application. Reasons are set forth below.

First, Example 2 of the application clearly teaches the synthetic procedure used to make the RGTA 1112 (CM₂DPheS₂) and RGTA 1113 (CM₃DTyrS₂) modified dextran polymers from dextran. In this synthesis dextran, a polymer comprised of glucose monomers, is carboxymethylated such that -CH₂COOH or -CH₂COO⁻ groups are attached to the glucose monomer. For RGTA 1112 (CM₂DPheS₂) synthesis this carboxymethylation step is performed two times and for RGTA 1113 (CM₃DTyrS₂) synthesis this carboxymethylation step is performed three times. The carboxymethylation occurs primarily at position 2 of glucose monomers in the dextran polymer, and only a certain percentage of the glucose monomers in the dextran polymer are substituted. A portion of the modified dextran polymer resulting from this carboxymethylation can be schematically represented as shown in the image below:



Thus, the modified dextran polymer resulting from this carboxymethylation comprises x_0 occurrences of the bracketed structure x_0 and n occurrences of the bracketed structure n , where $n+x_0$ equal the number of dextran units in the polymer.

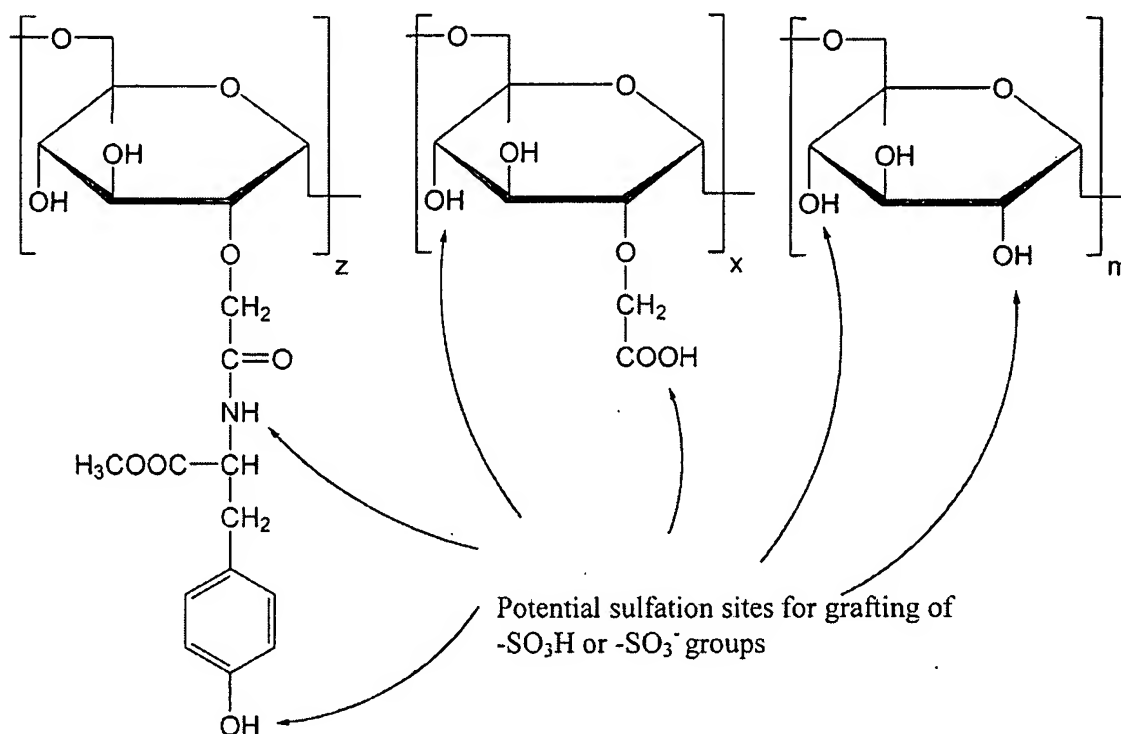
Next, as described in the paragraph spanning pages 34 and 35 through the second full paragraph on page 35, this carboxymethylated modified dextran polymer is functionalized with a group derived from the amino acid residue Tyr (tyrosine), or Phe (phenylalanine), which is reacted with the carboxymethyl groups in the modified dextran polymer. In the resulting modified dextran polymer, only a certain percentage of the carboxymethyl groups in the polymer are substituted with the tyrosine derived functional group or the phenylalanine derived functional group. When substituted with the tyrosine derived functional group, a portion of the resulting modified dextran polymer can be schematically represented as shown in the image below:



Thus, the modified dextran polymer resulting from this carboxymethylation comprises z occurrences of the bracketed structure z , x occurrences of the bracketed structure x , and m occurrences of the bracketed structure m , where $z+x+m$ equal the number of dextran units in the polymer.

A sulfation reaction is then performed on the modified dextran polymer using 2 equivalents of chlorosulfonic acid. During this reaction $-\text{SO}_3\text{H}$ or $-\text{SO}_3^-$ groups are grafted onto functional groups having acidic hydrogens (and replace these acidic hydrogens as shown in, for example, Fig. 9). Examples of such acidic hydrogen atoms include those in the $-\text{OH}$ groups and amide groups present on the monomer subunits of the modified dextran polymer. These

functional groups are identified in the image below and include hydroxyl groups present on the glucose monomer, the attached carboxymethyl groups ($-\text{CH}_2\text{COOH}$), the amide groups formed by substitution with the phenylalanine derived functional group, the amide groups formed by substitution with the tyrosine derived functional group and the hydroxyl group present on the tyrosine derived functional group. See also Fig. 9, Example 2 and Table II.



In the resulting modified dextran polymer, only a certain percentage of the reactive groups in the polymer are sulfated such that $-\text{SO}_3\text{H}$ or $-\text{SO}_3^-$ groups only become grafted onto a fraction of the potential reactive sites. Additionally, some reactive hydroxyl groups present in $-\text{COOH}$ functional groups will form unstable sulfuric anhydrides that will hydrolyze back to $-\text{COOH}$ functional groups when the sulfation reaction is quenched.

Second, it should be noted that the modified dextran polymers comprise monomer subunits having the formulas A, A-X, A-Y and A-Z. See e.g. the second full paragraph on page 9 and the third full paragraph on page 34 as well as Figs. 5 and 9. Stated differently, these polymers have the general formula $\text{A}_a\text{X}_x\text{Y}_y\text{Z}_z$ where the subscripted characters indicate the number of the A, X, Y and Z components in the polymer. See e.g. the paragraph spanning pages

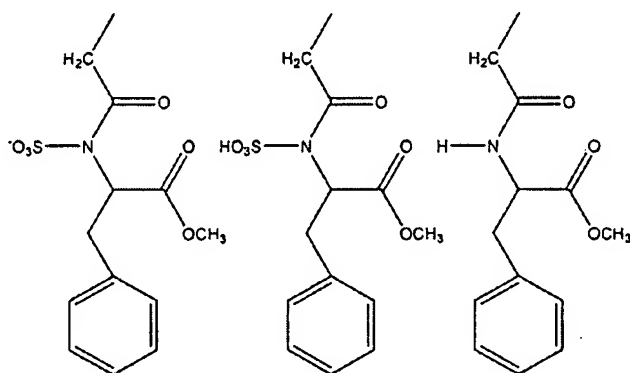
5 and 6 through the top of page 8 and the paragraph spanning pages 8 and 9 through the top of page 10.

As taught at the last full paragraph on page 7, Fig. 9 and Example 2 of the originally filed application, the monomer subunit "A" is a glucose monomer.

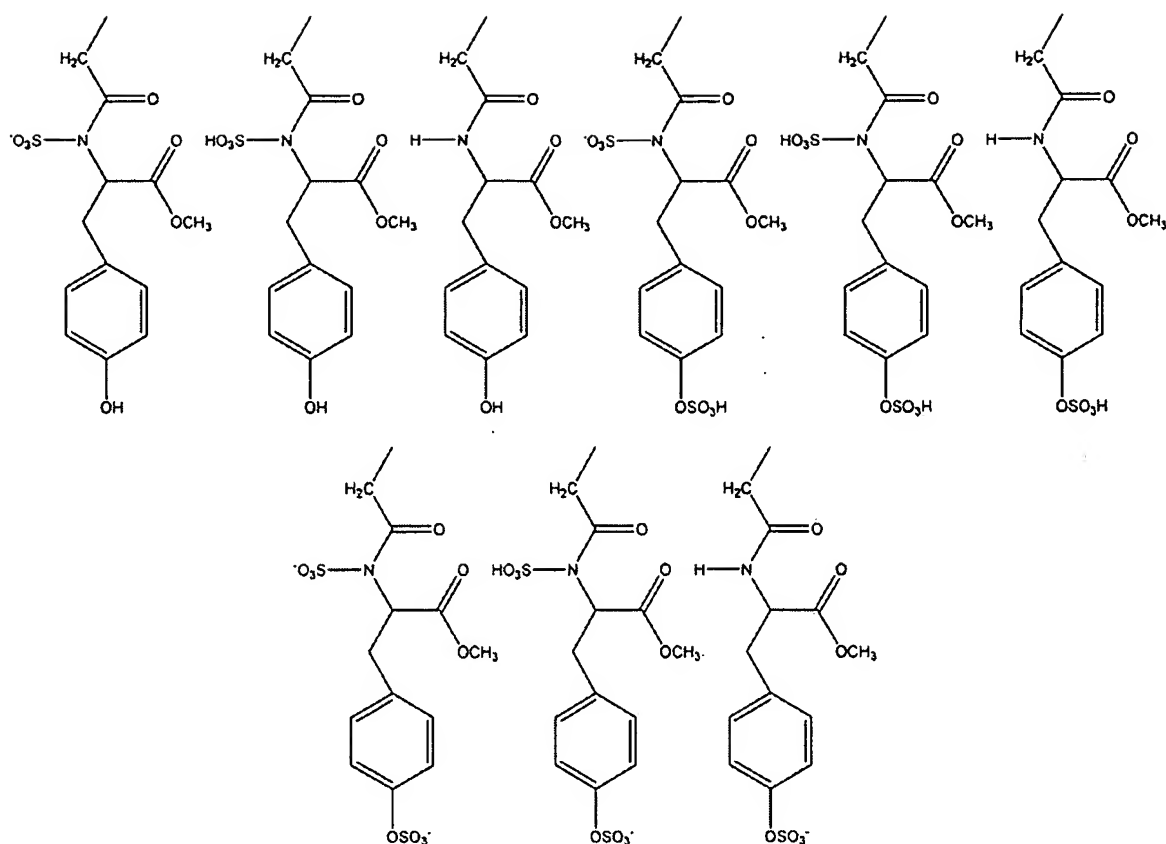
As taught at the paragraph spanning pages 5 and 6, "X" represents "a carboxyl group fixed on a monomer A and contained within a group according to...the formula: $-R-COO-R'$, in which R is...an aliphatic hydrocarbon chain...and R' represents a hydrogen atom or cation[.]" Thus, "X" can be $-CH_2-COOH$ or $-CH_2-COONa$ as taught in Example 2, the paragraph spanning pages 28 and 29. Additionally, as those of ordinary skill in the art would recognize, "X" can be $-CH_2-COO^-$ depending on the ionization state of the $-COOH$ or $-COONa$ functional groups in X. Together, this means "X" can be a salt of $-CH_2-COOH$ or $-CH_2-COO^-$ such as, for example, a salt comprising a Na^+ cation.

As taught at the paragraph spanning pages 5 and 6, "Y" represents a "sulfate or sulfonate group fixed on a monomer A and contained within a group according to one of the following formulas: $-R-O-SO_3-R'$, $-R-N-SO_3-R'$, $R-SO_3-R'$, in which R is a bond or an aliphatic hydrocarbon chain, possibly branched and/or unsaturated...and R' represents a hydrogen atom or cation[.]" Thus, "Y" can be at least one selected from the group consisting of $-SO_3H$, $-SO_3Na$ and $-SO_3^-$. Together, this means "Y" can be a salt of $-SO_3H$ or $-SO_3^-$ such as, for example, a salt comprising a Na^+ cation.

As taught at the paragraph spanning pages 8 and 9, "Z" represents a "functional chemical group" and "can be amino acids...or derivatives thereof." Thus, "Z" can be:



and salts thereof; and



and salts thereof;

as taught in Example 2, at the third full paragraph of page 34 and the second full paragraph on page 35, and Fig. 9. Stated differently Z can be a tyrosine or phenylalanine derivative residue, optionally substituted with Y, and linked to the glucose monomer A via a $-\text{CH}_2\text{C}(=\text{O})-$ bond. Importantly, these amino acid derivatives would be understood by one of ordinary skill in the art to necessarily result from the synthesis from dextran of the RGTA 1112 ($\text{CM}_2\text{DPheS}_2$) and RGTA 1113 ($\text{CM}_3\text{DTyrS}_2$) modified dextran polymers described in the application. As discussed above, in the context of “X” and “Y,” the $-\text{COOH}$, $-\text{COO}^-$, $-\text{SO}_3\text{H}$ and $-\text{SO}_3^-$ groups in the modified dextran polymers can, as those of ordinary skill in the art will recognize, form salts such as, for example, a salt comprising a Na^+ cation. Together, this means “Z” can be a salt of the tyrosine derivatives shown above or the phenylalanine derivatives shown above linked to the glucose monomer A such as, for example, a salt comprising a Na^+ cation.

Third, as discussed above, only a certain number of monomer subunits are modified at each step in the synthesis of the modified dextran polymers useful in the claimed methods. This is a function of the relative reactivity and the steric hindrance of these sites in the modified

dextran polymers. This means that it is also necessary to define the characteristics of modified dextran polymers RGTA 1112 (CM₂DPheS₂) and RGTA 1113 (CM₃DTyrS₂) in several other different ways.

The modified dextran polymers useful in the claimed methods can be defined in terms of the molecular mass of the modified polymers. The application teaches at the paragraph spanning pages 5 and 6 that “_a” represents “the number of monomers A, which is such that the mass of the polymers of formula (I) is greater than approximately 5,000 da[.]” Stated differently, the mass of the modified dextran polymer is greater than 5,000 Da.

The modified dextran polymers useful in the claimed methods can also be defined in terms of the substitution rate, or percentage, of the monomer subunits in the dextran polymer that bear a “X” group. The application teaches at the paragraph spanning pages 5 and 6 that “_x” represents “the substitution rate of the set of monomers A by the groups X[.]” Table II and the paragraph spanning pages 6 and 7 together teach that this substitution rate is statistically about 28.9% for modified dextran polymers comprising phenylalanine derivatives (*e.g.* the RGTA1112 (CM₂DPheS₂) modified dextran polymer). Table II and the paragraph spanning pages 6 and 7 together also teach that this substitution rate is statistically about 19.8% for modified dextran polymers comprising tyrosine derivatives (*e.g.* the RGTA1113 (CM₃DTyrS₂) modified dextran polymer).

The modified dextran polymers useful in the claimed methods can also be defined in terms of the substitution rate, or percentage, of the monomer subunits in the dextran polymer that bear a “Y” group. The application teaches at the paragraph spanning pages 5 and 6 that “_y” represents “the substitution rate of the set of monomers A by the groups Y[.]” Table II and the paragraph spanning pages 6 and 7 together teach that this substitution rate is statistically about 56.2% for modified dextran polymers comprising phenylalanine derivatives (*e.g.* the RGTA1112 (CM₂DPheS₂) modified dextran polymer). Table II and the paragraph spanning pages 6 and 7 together also teach that this substitution rate is statistically about 65.9% for modified dextran polymers comprising tyrosine derivatives (*e.g.* the RGTA1113 (CM₃DTyrS₂) modified dextran polymer).

The modified dextran polymers useful in the claimed methods can also be defined in terms of the substitution rate, or percentage, of the monomer subunits in the dextran polymer that bear a “Z” group. The application teaches at the paragraph spanning pages 8 and 9 that “_z”

represents “the substitution rate of the set of monomers A by the groups Z[.]” Table II and the paragraph spanning pages 6 and 7 together teach that this substitution rate is statistically about 17.9% for modified dextran polymers comprising phenylalanine derivatives (*e.g.* the RGTA1112 (CM₂DPhes₂) modified dextran polymer). Table II and the paragraph spanning pages 6 and 7 together also teach that this substitution rate is statistically about 28.9% for modified dextran polymers comprising tyrosine derivatives (*e.g.* the RGTA1113 (CM₃DTyrS₂) modified dextran polymer).

Fourth, Claim 65 has been amended to recite the “percentage of glucose monomers A that bear a” X, Y or Z group is “statistically about” the specific percentage values shown in Table II of the originally filed application. The Applicants note that the recitation of “statistically about” in Claim 65, while flexible, is sufficiently definite to satisfy the written description requirement of 35 USC §112. This is because the application teaches at the paragraph spanning pages 6 and 7 that:

In the definition of the substitution rates..., a substitution rate x of 100% is understood to mean that each monomer A of the polymer of the invention contains statistically one X group. Similarly, a substitution rate y of 100% is understood to mean that each monomer of the polymer of the invention contains statistically one Y group. Substitution rates higher than 100% manifest the fact that each monomer bears statistically more than one group of the type under consideration. Conversely, substitution rates lower than 100% manifest the fact that each monomer bears statistically less than one group of the type under consideration. [(emphasis added)]

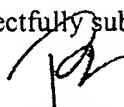
Furthermore, one of ordinary skill in the art would understand that the empirical methods (*e.g.* acid-base titration based functional group determinations, NMR analyses, *etc.*) used to measure the substitution rates of the various groups on the biocompatible polymers would necessarily require the application of appropriate statistical methods to describe the measurements produced by different analytical runs or the samples analyzed. Importantly, such statistical methods for the description of a collection of data are well known to those of ordinary skill in the art. *See e.g.* pages 38-40 of the originally filed application. Furthermore, amended Claim 65 includes many other limitations such that when the recitation of “statistically about” is considered in conjunction with all these other limitations it is clear that the amendments, *in toto*, render Claim 65 definite under 35 USC §112, second paragraph.

Thus, the above makes it clear one of ordinary skill in the art would recognize that the biocompatible biopolymer defined in amended Claim 65 describes the RGTA1112 (CM₂DPheS₂) and RGTA1113 (CM₃DTyrS₂) modified dextran polymers produced via the synthetic process described in Example 2 of the originally filed application.

The Applicants respectfully request the withdrawal of the rejection under 35 USC §112, second paragraph.

In light of the foregoing, the Applicants respectfully submit that the entire application is in condition for allowance, which is respectfully requested.

Respectfully submitted,



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